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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants	: C. Carling, et al.	
Serial No.	: 08/317,407	Examiner : R. Henley, III
Filed	: October 3, 1994	Group Art Unit : 1205
For	: COMBINATION OF A BRONCHODILATOR AND STEROIDAL ANTI-INFLAMMATORY DRUG FOR THE TREATMENT OF RESPIRATORY DISORDERS, AS WELL AS ITS USE AND THE PREPARATION THEREOF	

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JUN 12 1995

I hereby certify that this paper is being facsimile transmitted to: The Assistant Commissioner for Patents, Washington, D.C. 20231, on June 9, 1995.

Richard J. Sterner — Agent Name

35,372 — PTO Reg. No.

Richard J. Sterner — Signature

June 9, 1995 — Date of Signature

Facsimile No.: 703-308-4556
Number of Pages 28
Attention: Examiner R. Henley, III

The Assistant Commissioner for Patents
Washington, D.C. 20231

TRANSMITTAL OF DECLARATION UNDER 37 C.F.R. § 1.132

Sir:

This communication is a follow-up to Applicants' May 23, 1995 Amendment and Response and the telephone conversation between the Examiner and Applicants' agent on May 25, 1995.

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In the May 23, 1995 Amendment and Response, it was stated that a Declaration under 37 C.F.R. § 1.32 would be submitted in due course in support of the nonobviousness of the instant invention over the cited prior art. Accordingly, Applicants submit herewith the Declaration of Dr. Jan W. Trofast. In the May 25, 1995 conversation with Applicants' agent, the Examiner indicated that full consideration would be given to the Declaration in combination with the May 23, 1995 Amendment and Response.

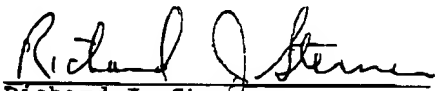
The enclosed Declaration sets forth data demonstrating the unexpected efficacy of the claimed formoterol-budesonide combinations in a range of dosages; the data provide sufficient enablement for the scope of the invention as claimed. The Declaration further includes material corroborating the validity of the tests performed in demonstrating the claimed utility of the inventive formoterol-budesonide combinations.

It is submitted that the enclosed Declaration in conjunction with the May 23, 1995 Amendment and Response is sufficient to overcome the outstanding prior art rejection of the claims. Reconsideration and allowance of pending claims 1, 2, 7 and 14-23 are respectfully requested.

The Assistant Commissioner is hereby authorized to charge any fees due in connection with this communication to Deposit Account No. 23-1703.

Dated: June 9, 1995

Respectfully submitted,



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Enclosure

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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DECLARATION UNDER 37 C.F.R. § 1.132

I, Jan William Trofast, Ph.D., declare as follows:

I am Principal Research Scientist in Pharmaceutical and Analytical Research and Development at Astra Draco AB in Lund, Sweden, a subsidiary of Astra AB, the assignee of the above-identified application. My curriculum vitae is attached as Exhibit A.

I am a coinventor of the subject matter of the above-identified patent application, and I participated in the August 17, 1994 Examiner interview. I am familiar with the office actions issued during the course of prosecution of this application and its parent, as well as the prior art patents of Brattsand, et al. and Murakami, et al. cited against the pending claims. The pharmacological *in vivo*

studies set forth below were carried out at my behest by pharmacologists at Astra Draco AB.

The tests were performed to determine the effect of a fixed combination of budesonide and formoterol on the inhibition of lung inflammation. The test model employed was the Sephadex-induced edema model. The model is well established in the field and widely recognized as universally predictive of anti-inflammatory properties, as attested to by a number of published articles. Three representative articles (Källström, et al., Agents and Actions 17, 355-357 (1985); Kubin, et al., Int. Arch. Allergy Immunol. 98, 266-272 (1992) and Brattsand, et al., Int. J. Microcirc. Clin. Exp. 5, 263 (1986)) are attached hereto as Exhibit B.

Sephadex was administered intratracheally to Sprague-Dawley rats together with saline (first control), budesonide, formoterol, or budesonide-formoterol combinations in various budesonide-formoterol concentration ratios. Either six or twelve animals were subjected to each experimental regimen as indicated in Table I below. The animals were sacrificed the following day, their lungs excised and the inflammatory process measured as lung weight increase due to edema.

The weight increase of lungs removed from animals subjected to the Sephadex-saline regimen compared to the weight of lungs removed from a second group of control animals, to which only saline (i.e., neither Sephadex nor any test compound) was administered, was taken as representative of maximum Sephadex-induced edema. Inhibition of the Sephadex-induced lung edema by a test substance was determined as per cent reduction of induced edema in the presence of the test compound compared to the maximum edema induced in the Sephadex-saline controls. The results are presented in Table I below:

TABLE I

Inhibition of Sephadex-Induced Lung Inflammation in Rats

Compound	Amount Administered (nmol/kg)	n†	% inhibition
1. Formoterol	5	6	21.0
2. Budesonide	5	6	3.1
3. Formoterol + Budesonide (1:1)	5 + 5	6	42.1
4. Formoterol	2	12	13
5. Budesonide	10	12	-14
6. Formoterol + Budesonide (1:5)	2 + 10	12	28*
7. Budesonide	20	12	-9
8. Formoterol + Budesonide (1:10)	2 + 20	12	52**
9. Budesonide	40	12	9
10. Formoterol + Budesonide (1:20)	2 + 40	12	66**

† number of animals subjected to regimen

Statistical parameters: * $p<0.05$; ** $p<0.01$

Comparison with Sephadex-induced inflammation in control animals showed that neither budesonide (at any of the four administered concentrations) without formoterol nor formoterol (at either of the two administered concentrations) without budesonide significantly inhibited the induced edema, based on the criterion of the Wilcoxon rank sum test. Furthermore, even the sum of the individual

effects would not be considered significant by this criterion.

By comparison, several fixed molar ratios of formoterol to budesonide given in combination (1:5 ratio, 28% inhibition; 1:10 ratio, 52% inhibition; 1:20 ratio, 66% inhibition) showed significant reduction of lung edema in the Sephadex model as judged by the criterion of the Wilcoxon rank sum test. In these tests performed with formoterol-budesonide combinations, the statistical analysis was obtained by comparing the effect of a given combination with the effect of the corresponding amount of budesonide administered without formoterol. This type of analysis was designed to particularly point up enhanced anti-inflammatory effects of the combination in comparison to the effects expected (and observed) for the anti-inflammatory steroid (budesonide) component alone.

None of the values observed, whether positive or negative, for inhibition of Sephadex-induced inflammation by budesonide alone are statistically significant. All such values simply demonstrate that budesonide at the concentrations administered is ineffective in reducing inflammation. This is in keeping with what would be predicted from the known pharmacology of budesonide; concentrations of the steroid in the range from 5 nmol/kg

to 40 nmol/kg, as in the tests described herein, would not be expected to demonstrate significant anti-inflammatory effect in rats. However, as the data of Table I show, budesonide-formoterol combinations provided significant reduction of inflammation, even though the concentration of budesonide administered remained in the 5-40 nmol/kg range.

It is known in the pharmacology art that rat cells exhibit 3-10 times greater sensitivity to glucocorticosteroids than does man, although this could differ to some extent in *in vivo* test models. The administration of a 1:1 molar ratio of formoterol to budesonide in the test regimen is reflective of this expected greater sensitivity in the rat. It can be seen from the test data (obtained from 6 test animals for each experimental condition) on line 3 of Table I that budesonide and formoterol administered together at this molar ratio are also highly effective (42.1% inhibition) in reducing Sephadex-induced lung edema.

The administered 1:5, 1:10 and 1:20 molar ratios of formoterol to budesonide are more reflective of the types of ratios that one of skill in the art would envision using in humans, given the lower sensitivity of man to the budesonide component. As pointed out above, these ratios,

in testing in a larger number of animals, were seen to be highly effective in reducing lung inflammation.

The data demonstrate that budesonide-formoterol combinations over a range of molar ratios provide an enhancement of anti-inflammatory effect which, unexpectedly, is significantly greater than the sum of the individual anti-inflammatory effects of the two active agents. More precisely, neither budesonide without formoterol nor formoterol without budesonide provided significant reduction of Sephadex-induced inflammation at the administered concentrations, whereas treatment of animals with the combined agents in the same concentrations administered individually resulted in significant reduction of inflammation. The unexpected effects were seen for combinations more appropriate for the known pharmacology of the active agents in rats, as well as for combinations more appropriate for known human pharmacology.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true and further, that these statements were made with the knowledge

that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Date: dated 24 May 1995

Jan W. Trofast

JAN W. TROFAST, Ph.D.